(12) INTERNATIONAL

LICATION PUBLISHED UNDER THE PATENT COPPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



# 

(43) International Publication Date 3 June 2004 (03.06.2004)

PCT

### (10) International Publication Number WO 2004/046119 A1

(51) International Patent Classification<sup>7</sup>: C07D 239/91. 279/16, 413/04, 265/38, 209/86, 215/14, 209/08, 213/30, 207/32, 235/06, 409/04, 261/08, 405/04, A61K 31/421,

31/422, 31/47, 31/358, 31/4439, C07C 43/03, A61P 3/10

(21) International Application Number:

PCT/IN2003/000358

(22) International Filing Date:

14 November 2003 (14.11.2003)

(25) Filing Language:

English

(26) Publication Language:

**English** 

(30) Priority Data: 992/MUM/2002 15 November 2002 (15.11.2002) 792/MUM/2003 12 August 2003 (12.08.2003) IN

IN

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED ARALKYL DERIVATIVES

 $A-(CH_2)_n-X-A_1$   $G_2$ 

 $A-(CH_2)_n-X-Ar$ 

(57) Abstract: The present invention relates to novel substituted aralkyl derivatives of the general formula (I) & (IIIa), their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, pharmaceutical compositions containing them, use of these compounds in medicine and the intermediates involved in their preparation.

Present Application No Present 03/00358

A. CLASSIFICATION OF SUBJECT MALZER

IPC 7 C07D239/91 C07D279/16 C07D413/04 C07D265/38 C07D209/86

C07D215/14 C07D209/08 C07D213/30 C07D207/32 C07D235/06

C07D409/04 C07D261/08 C07D405/04 A61K31/421 A61K31/422

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
Υ .	WO 91/19702 A (PFIZER) 26 December 1991 (1991-12-26) see general formula II, especially definitions of Z and Z'	9-22	
Υ	EP 0 930 299 A (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21) cited in the application see definition of R' and examples 23,13.	9-22	
E	WO 2004/031162 A (HOFFMANN LA ROCHE) 15 April 2004 (2004-04-15) see defintions of R3 and R4	1-22	
P,Y	WO 02/092084 A (HOFFMANN LA ROCHE) 21 November 2002 (2002-11-21) cited in the application see defintions of R2,R3,R4,R6	1-22	
	-/		

X Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
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Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2004	11/05/2004
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

national Application No

A. CLASSIFICATION OF SUBJECT MA 17538 A61K31/4439 C07C43/03

A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	EGBERTSON M S ET AL: "NON-PEPTIDE FIBRINOGEN RECEPTOR ANTAGONISTS. 2. OPTIMIZATION OF A TYROSINE TEMPLATE AS A MIMIC FOR ARG-GLY-ASP" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 16, 1994, pages 2537-2551, XP000574969 ISSN: 0022-2623 see examples 24a and 17	1,2,4,7, 8,14,15			
E	WO 2004/004665 A (DEVASTHALE PRATIK; SQUIBB BRISTOL MYERS CO (US); CHEN SEAN (US); Y) 15 January 2004 (2004-01-15) see RN 647006-18-6 and RN 647006-17-5	1-4			

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<ul> <li>Special categories of cited documents:</li> <li>"A" document defining the general state of the art which is not considered to be of particular relevance</li> <li>"E" earlier document but published on or after the international filling date</li> <li>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>"O" document referring to an oral disclosure, use, exhibition or other means</li> <li>"P" document published prior to the international filling date but later than the priority date claimed</li> <li>Date of the actual completion of the International search</li> <li>4 May 2004</li> </ul>	<ul> <li>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</li> <li>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>*&amp;* document member of the same patent family</li> <li>Date of maiting of the international search report</li> </ul>
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  Fax: (+31-70) 340-3016	Authorized officer  Scruton-Evans, I

PCTAIN 03/00358

C.(Continu	ation) DOCUMENTS CONS	PC N 03/00358
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Retevant to claim No.
		nesevani io ciaim no.
P,Y	WO 03/072102 A (CONNER SCOTT EUGENE; MANTLO NATHAN BRYAN (US); LILLY CO ELI (US);) 4 September 2003 (2003-09-04) see definitions of Q,R3/R4 and A and example 38	1-22
X	JP 51 149265 A (YOSHITOMI PHARMACEUT IND LTD) 22 December 1976 (1976-12-22) RN 62803-01-4	1
X	EP 0 478 363 A (MERCK & CO INC) 1 April 1992 (1992-04-01) see compound 7-4, page 34 and experimental, page 35, lines 45-50	1-4
Y	WO 96/38415 A (SUMITOMO METAL IND ;TAKENO HIDEKAZU (JP); IKEMOTO TOMOYUKI (JP); S) 5 December 1996 (1996-12-05)	1-22
X	RN 185679-52-1	1-4,7,8, 14,15
	WO 01/40170 A (ASTRAZENECA AB ;FAEGERHAG JONAS (SE); LI LANNA (SE); LINDSTEDT ALS) 7 June 2001 (2001-06-07) cited in the application especially definitions of A the whole document	1-22



Вохі	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
<del></del> -	· · · · · · · · · · · · · · · · · · ·
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Although claims 17-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. 🗓	Claims Nos.: 1-5 (partly), 7,8 (partly), 14-22 (partly) because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
	see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	mational Searching Authority found multiple inventions in this international application, as follows:
	a approximate to the second se
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
1	of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4 ;	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is estricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark o	The additional search tees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.

International Application No. PCT/ IN 03 /00358

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5 (partly),7,8 (partly),14-22 (partly)

Present claims 1-5,7,8,14-22 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I wherein A is a heterocycle, Ar is a 1,4-phenylene and X is O, and all of the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

reational Application No

cite	atent document ed in search report		Publication date		Patent family member(s)		Publication date
WC	9119702	Α	26-12-1991	US	5089514	A	18-02-1992
				AT	149156		15-03-1997
				AU	646052	<b>B2</b>	03-02-1994
				AU	7995691	Α	07-01-1992
				CA	2084898	A1	15-12-199
				DE	69124798	D1	03-04-1997
				DE	69124798	T2	12-06-1997
				DK	533781	T3	07-07-1997
				EP	0533781	A1	31-03-1993
				ES	2098356	T3	01-05-1997
				FI	925640		11-12-1992
				GR	3022714		30-06-1997
				HU	65603		28-07-1994
				ΙE	912003		18-12-1991
				IL	98447		31-12-1995
				JP	2581523		12-02-1997
			•	JP	7149636		13-06-1995
				JP	7005513		25-01-1995
				JP	5507920		11-11-1993
				NO	924799		14-12-1992
				NZ	238528		27-07-1993
				PT	97950		31-03-1992
				WO	9119702		26-12-1991
				US	5438074		01-08-1995
				US	5306726		26-04-1994
				ZA 	9104519	A 	27-01-1993
EP	0930299	Α	21-07-1999	JP	3215048		02-10-2001
				JP	9323982		16-12-1997
				AU	740444		01-11-2001
				AU	3866597		06-03-1998
				BG	103268		29-12-2000
				BR	9711627		24-08-1999
				CA	2263721		26-02-1998
				EE	9900069		15-10-1999
				EP	0930299	AI	21-07-1999
				NO NZ	990700		19-04-1999
				NZ PL	334738		26-01-2001
				SK	331861 21099		16-08-1999
				US	6204277		16-05-2000
				CN	1233241		20-03-2001
				CZ	9900536		27-10-1999
				WO	9807699		14-07-1999 26-02-1998
WO	2004031162	Α	15-04-2004	WO	2004031162	A1	15-04-2004
W0	02092084	Α	21-11-2002	CA	2445145	Δ1	
		• •	-I II 2002	WO	02092084		21-11-2002
				EP	1392295		21-11-2002
				NO	20035086		03-03-2004
				US	2003055265		14-11-2003 20-03-2003
							20-03-2003 
WO	2004004665	Α	15-01-2004	WO	2004004665		15-01-2004
				US	2004063700	A1	01-04-2004
WO	03072102	Α	04-09-2003	WO	03072102	A1	04-09-2003

reTIN 03/00358

 Pa cited	atent document d in search report		Publication date		Patent family member(s)	Publication date
JP	51149265	Α	22-12-1976	NONE		
EP	0478363	Α	01-04-1992	AT	150454 T	1F 04 1007
		,,	01 04 1552	AU	655436 B2	15-04-1997
				AU	8478291 A	22-12-1994
				CA	2052073 A1	02-04-1992
				CY		28-03-1992
				DE	2048 A 69125235 D1	30-04-1998
				DE		24-04-1997
				DK	69125235 T2	07-08-1997
				EP	478363 T3 0478363 A2	12-05-1997
				EP		01-04-1992
				ES	0743302 A2	20-11-1996
				ES ES	2100214 T3	16-06-1997
				FI	2133892 T3	16-09-1999
					914534 A	28-03-1992
				FI	20011201 A	06-06-2001
				GR	3023226 T3	30-07-1997
				GR	3031473 T3	31-01-2000
				HK	1000509 A1	03-04-1998
				HR	930779 A1	28-02-1997
				IE IL	913383 A1	08-04-1992
					99540 A	31-07-1995
				JP	2812431 B2	22-10-1998
				JP	9132558 A	20-05-1997
				JP	4288051 A	13-10-1992
				JP	7094425 B	11-10-1995
				KR	216939 B1	01-09-1999
				LU	90505 A9	20-03-2000
				LV	5746 A4	20-10-1996
				LV	12089 A	20-07-1998
				LV	12089 B	20-11-1998
				NO	913784 A ,B,	30-03-1992
				NZ	239846 A	25-11-1994
				PT	99098 A ,B	31-08-1992
				SG	63636 A1	30-03-1999
				SI	9210306 A ,B	31-08-1995
				WO	9319046 A1	30-09-1993
				US	5880136 A	09-03-1999
				US	6040317 A	21-03-2000
				บร	5658929 A	19-08-1997
				US	5292756 A	08-03-1994
				US	5814643 A	29-09-1998
				ZA	9107661 A	27-05-1992
				CN	1069971 A ,B	17-03-1993
WO 9	9638415	Α	05-12-1996	JP	8325263 A	10-12-1996
				AU	5779196 A	18-12-1996
				WO	9638415 A1	05-12-1996
WO (	0140170	Α	07-06-2001	AU	766547 B2	16-10-2003
				AU	2240101 A	12-06-2001
				BR	0016133 A	20-08-2002
				CA	2392035 A1	07-06-2001
				CN	1433401 T	30-07-2003
				EP	1237857 A1	11-09-2002
					2003515581 T	07-05-2003
				NO	20022603 A	10-07-2002
				NZ	518922 A	28-11-2003

national Application No

INTERNA	ATIONAL SEARCH	rcTLIN 03/00358		
Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0140170	A	WO US 2 ZA	0140170 A1 2003018207 A1 200203703 A	07-06-2001 23-01-2003 11-08-2003